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BC 268.42.048

From: Brannock, Michael
Sent: Monday, September 17, 2001 11:09 AM
T: STIC-ILL
Subject: 09378759

Please provide the following refs:

Pasquale et al., Cell Regulation 2(7)523-34, July 1991

Chan et al., Oncogene 6(6)1057-61, 1991

Thank you

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eeek and *erk*, new members of the *eph* subclass of receptor protein-tyrosine kinases

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We have identified human and rat DNAs encoding two novel members of the *eph* subclass of putative receptor protein-tyrosine kinases. Rat cDNA clones encoding *eeek* (*eph*- and *elk*-related kinase) were isolated from a brain cDNA library probed with DNA encoding the kinase region of the insulin receptor-related receptor. The predicted *eeek* protein contains all the amino acid residues conserved in the catalytic domains of protein-tyrosine kinases and is most similar to two putative receptor protein-tyrosine kinases of the *eph* subclass, *elk* (69%) and *eph* (57%). Human genomic DNAs encoding part of *eeek* (*EEK*) as well as another putative protein-tyrosine kinase most similar to *elk* (90%), *ERK* (*elk*-related kinase), were isolated and partially characterized. The novel identity of these two *eph*-family genes was further supported by Southern blot analyses and localization to human chromosome 1. In Northern blot analysis of rat RNA, DNAs encoding rat *eeek* and human *ERK* hybridized to transcripts most abundant in brain and lung, respectively. These two new members of the *eph* subclass of receptor protein-tyrosine kinases, *eeek* and *erk*, may therefore have tissue-specific functions distinct from those of other *eph* family members.

Introduction

Protein-tyrosine kinases (PTKs) are structurally and functionally related enzymes intimately involved in signal transduction. Initially discovered as transforming proteins of acutely oncogenic retroviruses (Hunter & Cooper, 1985), altered versions of cellular PTKs have since been implicated in the etiology of certain human malignancies (e.g., Konopka *et al.*, 1984; Martin-Zanca *et al.*, 1986). Under physiological conditions, some PTKs function as receptors for a variety of hormones and growth factors to alter such diverse cellular processes as metabolism, growth and differentiation (Yarden & Ullrich, 1988). Ligand binding to the extracellular region of receptor PTKs somehow activates the cytoplasmic catalytic domain to phosphorylate specific substrates such as the GTPase activating protein (GAP, Kazanietz *et al.*, 1990), phospholipase C (Meisenhelder *et al.*, 1989) and phosphatidylinositol 3-kinase (Auger *et al.*, 1989).

Receptor PTK subclasses, defined on the basis of structural similarity (Hanks *et al.*, 1988; Yarden & Ullrich, 1988; Ullrich & Schlessinger, 1990), include those of the epidermal growth factor receptor (EGFR), the insulin receptor (IR), and the platelet-derived and

fibroblast growth factor receptors (PDGFR, FGFR). Within these subclasses are putative receptor PTKs whose presumptive ligands are unknown (Hanks *et al.*, 1988; Ullrich & Schlessinger, 1990). Insight into the function of these putative receptors will be facilitated if, as expected, family members that exhibit limited divergence play similar roles in cellular physiology (Hanks *et al.*, 1988). It is likely, however, that the elucidation of the functional roles of these PTKs will continue to be outpaced by their rate of discovery.

The *eph* PTK defined a new receptor PTK subclass (Hirai *et al.*, 1987) which on the basis of structural similarity also includes *elk* (Letwin *et al.*, 1988). The *eph* full-length cDNA predicts a transmembrane receptor PTK featuring a single Cys-rich region in the extracellular domain and an uninterrupted PTK domain (Hirai *et al.*, 1987). Two lines of evidence suggest that *eph* may be involved in oncogenesis: *eph* is overexpressed in several human carcinomas (Hirai *et al.*, 1987; Maru *et al.*, 1988); and overexpression of the *eph* gene enabled NIH3T3 cells to form tumors in nude mice and colonies in soft agar (Maru *et al.*, 1990).

We report the isolation and characterization of rat cDNA clones encoding a novel PTK, *eeek*, whose predicted amino acid sequence within its kinase domain exhibits extensive similarity with the sequence of receptors belonging to the *eph* subclass of PTKs. Human DNAs encoding *eeek* (*EEK*) as well as another novel member of the *eph* subclass, *erk*, have been isolated and used to localize both the *EEK* and *ERK* genes to human chromosome 1. The tissue-specific expression of these two new members of the *eph* subclass of receptor PTKs is distinct from other known members of the *eph* family; *eeek* expression is brain-specific and *erk* mRNA is most abundant in lung.

Results and discussion

To identify previously unknown PTKs, we used a DNA probe encoding the kinase region of the insulin receptor-related receptor (IRR, Shier & Watt, 1989) to screen at reduced stringency a rat brain cDNA library. PTKs are abundant in the central nervous system and have been implicated in such brain-specific functions as myelination and neuronal differentiation (Nairn *et al.*, 1985; Edwards *et al.*, 1988). Nucleotide sequence analysis of the entire insert DNA (867 bp) of one cDNA clone which hybridized with the IRR probe, *λ*reek.18, revealed a single open reading frame encoding 289 amino acids. Subsequent screening of another rat brain cDNA library with the insert DNA of *λ*reek.18 identified an overlapping clone, *λ*reek.32, that extended the sequence 3' by 249 nucleotides to a stop codon and a further 1.7 kb to a putative polyadenylation signal. The

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Received 7 May 1990; accepted in revised form 4 February 1991

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		▼D1	
reek	RIHIEKI I GS G ES G EV C YGR L QVP G Q R DVP V A I K A L K AGYTERQR	45	
relk	FVK..EV..A..F...YK...KL..K.EIY....T.....S.K..	58	
heph	WLMVDTV..E..F...YR.T.RL.S.DCKT....T..DTSPGG.W	675	
herkT..S....KN.	13	
		▼D2	
heek	QDFLR E AAIM G QFDHP N IIRLEGVVTRGRLAMIVTEY M ENGSLDA	17	
reek	R...S..S.....KS.PV..I..F....A..S	90	
relk	WN.....T.....S..H.LH.....KRKPI..I..F...AA...	103	
heph	R...S..S..... V .H.....KSTPV..I..F.....S	720	
herk	58	
		▼D3	
heek	FLRTHDGQFTILQLV G ML K GV G AG M RY L SD L GY I HR D LAARNILV	20	
reek	...QN.....VI.....R.IA...K...EMN.V.....	135	
relk	...ERED.LVPG...A..Q.IAS..N...NHN.V.....	148	
heph	...	765	
herk	...	61	
		▼D4	
reek	DGRLVCK V S D F G LSRALEDD-PEAA T TA-GGKI P IR W TA P EAIA	178	
relk	NSN.....Y.Q..TSDPT..SSL.....V.....	193	
heph	NQN.C.....T.L.D.--FDGT.E.Q-.....	807	
		▼D5	
reek	FRTFSSAS D V W S F G V M WEVLAYGERPYWNMTNQDV I SSVEEGYR	223	
relk	Y.K.T.....Y. IMSF.....D.S.....NAI.QD..	238	
heph	H.I.TT..... ISF.DK..GE.S..E.MK.I.D...	852	
reek	LPAPMGCPRALHQL M LDCWHK D RA Q RPRFSHVVS V LEALVHSPES	268	
relk	..P..D..A.....Q...NS....AEI.NT.DKMIRN.A.	283	
heph	..P.VD..AP.YE..KN..AY...R..H.QKLQAH..Q.LAN.H.	897	
reek	LRATATVSRCPA-PAFARSCFDLR--AGGNGNGDLTVGDWLD S IR	310	
relk	.KTV..ITAV.SQ.LLD...--IPDFT.FT-----..D...SA.K	320	
heph	..TI.NFD-----P.VTLR.PSL S .SD.IPYR..SE..E...	915	
reek	MGRYRDHFAAGGYSS L GMVLHMNAQDVRA L GITLMGHQ K KILGSI	355	
relk	.VQ...S.LTA.FT..QL.TQ.TSE.LLRI.V..A.....S..	366	
heph	.K..IL..HSA.LDTMEC..ELT.E.LTQM....P....R..C..	981	
reek	QTMRSQLSCTQ G PRRHL	372	
relk	HS..VQMNQSP S VMA	380	
heph	.GFKD	984	

Figure 1 Predicted amino acid sequences of rat *EEK*, human *EEK*, and human *ERK*, aligned with those of the closely related rat *ELK* (Letwin *et al.*, 1988) and human *EPH* (Hirai *et al.*, 1987). The rat *EEK* sequence numbered from 1 is from λ EEK.18 with the addition of the 3'-most 83 amino acids from λ EEK.32. Sequences were aligned using the GAP programme from the University of Wisconsin Genetics Computer Group Sequence Analysis Software Package. Bold letters represent amino acids conserved among kinases (Hanks *et al.*, 1988). Dots replace residues which are identical to the corresponding residues in the rat *EEK* sequence. Hyphens represent gaps introduced in sequences to maximize alignment. Triangles demarcate exons D1 to D5 of the *EPH* gene (Maru *et al.*, 1988): closed, conserved among *EPH* family members where known; open, not conserved. The nucleotide sequences for rat *EEK*, human *EEK* and human *ERK* have been submitted to the GenBank™/EMBL Data Bank with accession numbers X59290, X59291, and X59292.

composite predicted protein (Figure 1) contains all the amino acid residues conserved in the catalytic domains of PTKs (Hanks *et al.*, 1988) including the potential ATP binding site (Gly⁹-X-Gly-X-X-Gly¹⁴ and Lys³⁴). In addition, two sequences (Asp¹²⁷-Leu-(Ala-Ala-Arg)-Asn¹³² and Pro¹⁶⁸-Ile-Arg-Trp-Thr-Ala-Pro-Glu¹⁷⁵, Figure 1) specifically conserved in tyrosine rather than serine/threonine kinases as well as a potential phosphorylation site, Tyr¹⁶⁰, at a position analogous to the major aut phosphorylation site in pp60^{src} (Smart *et*

al., 1981), are also present. A computer search of sequence databases (EMBL, GenBank and SWISS-PROT, December 1990) revealed that we had identified a novel protein that exhibits striking amino acid similarity in its kinase domain to members of the *EPH* subclass of receptor PTKs, *ELK* and *EPH* (69% and 57% identity, respectively; also see Figure 1). This putative PTK is less similar to PTKs of other receptor as well as non-receptor subclasses: ~32% to 34% identity to representative members of the IR, EGFR, PDGFR, and

EGFR subclasses; and ~40% to 43% with those of the *abl*, and *fps/fes* subclasses (Figure 1; Hanks *et al.*, 1983; Kornbluth *et al.*, 1988). The similarity between *eeek* and the other *epk* family members, *epk* and *elk*, also extends into the carboxy-terminal tail (~43% identity, also see Figure 1), the region thought to exert negative control over receptor PTK signalling function (Ullrich & Schlessinger, 1990). Therefore, we have named this novel putative PTK *eeek*, for *epk*- and *elk*-related kinase.

Southern blot analysis of human genomic DNA revealed that a rat *eeek* cDNA probe hybridized at reduced stringency to multiple fragments in each digest (Figure 2A), suggesting that this rat *eeek* probe could identify several *eeek*-related human DNA sequences. At the highest stringency at which any hybridization was observed with the rat *eeek* cDNA probe, two human fragments were detected in each digest (Figure 2B). Hybridization with a rat *elk* cDNA probe (Letwin *et al.*, 1988) indicated that one of these fragments encoded the human homologue of rat *elk* (Figure 2C). To confirm that the other hybridizing fragment was the human homologue of rat *eeek*, we used rat *eeek* cDNA as probe to isolate part of the human *eeek* gene (*EEK*) from a human genomic library. The region of human *EEK* homologous to the rat *eeek* cDNA probe hybridized selectively to the fragments detected under high stringency by rat *eeek* DNA (Figure 2B, D) that had not hybridized with rat *elk* DNA (Figure 2C).

Nucleotide sequence analysis of an ~1 kb fragment of human *EEK* genomic DNA that hybridized with the rat *eeek* cDNA probe identified an exon which exhibits high identity with the rat *eeek* cDNA (95% amino acid, 92% nucleic acid, Figure 1) and much less similarity with its closest known relative, *elk* (70% amino acid, 71% nucleic acid, Letwin *et al.*, 1988). This *EEK* exon corresponds to amino acid residues 74 to 93 of the rat *eeek* cDNA (Figure 1) and to the analogous kinase domain exon D2 of the *epk* gene (Maru *et al.*, 1988). The position of both intron/exon junctions of *EEK* exon D2 (gccgccccagGC...GGgtgcgt), which are similar to the consensus acceptor and donor splice sites (Breathnach & Chambon, 1981), are conserved between *EEK* and the *epk* gene. Other genes encoding PTKs of the same subclass, such as the *src* (Maru *et al.*, 1988) and the *IR* (Shier & Watt, 1989) subclasses, have also been reported to exhibit conserved exon/intron organization throughout the entire kinase domain.

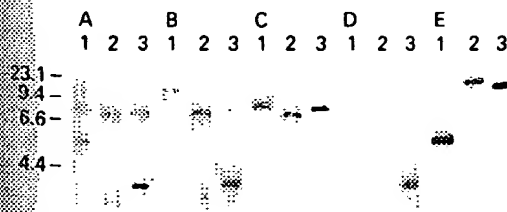


Figure 2 Southern blot analysis of genes encoding members of the *epk* family. Human genomic DNA was digested with EcoRI (lane 1), HindIII (lane 2) or BglII (lane 3). Filters were hybridized with a rat *eeek* cDNA probe (r*eeek*.D123p, a 246 bp PstI fragment encoding amino acid residues 22 to 103, Figure 1) and washed at 42°C (A) or at 60°C (B); with a rat *elk* cDNA probe (nucleotides 1-203, Letwin *et al.*, 1988; encoding amino acid residues 1-102, see Figure 1) (C), with human *EEK* genomic DNA (h*EEK*.D2p, an ~1.1 kb PstI fragment encoding D2) (D), or with human *ERK* genomic DNA (h*ERK*.D12e, an ~400 bp EcoRI fragment encoding part of D1 and all of D2) (E) and washed at 60-62°C.

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We also isolated another recombinant phage that contained human DNA which hybridized selectively to human genomic fragments (Figure 2E) detected only at reduced stringency by the rat *eeek* cDNA probe (Figure 2A). Analysis of the nucleotide sequence of this human isolate revealed that it was most closely related to the *epk* subclass member, *elk* (Letwin *et al.*, 1988); we have named it *erk* for *elk*-related kinase. Over the coding region sequenced, the human *ERK* fragment exhibited high identity (90% amino acid, 81% nucleic acid) with the rat *elk* cDNA (Letwin *et al.*, 1988) and lower identity with its next closest known relative, rat *eeek* (74% amino acid, 76% nucleic acid, Figure 1). This human *ERK* genomic fragment (~400 bp from the linker to an internal EcoRI site) contains a single exon corresponding to part of exon D1 as well as all of exon D2 of the *epk* gene (Maru *et al.*, 1988). The predicted splice junction at the end of exon D2 (CGGgttaggg) is similar to the consensus donor splice site (Breathnach & Chambon, 1981). The lack of an intron between exons D1 and D2 in the *ERK* gene was somewhat unexpected given that this intron is conserved between the genes encoding both *eeek* (Figure 1) and *epk* (Maru *et al.*, 1988). Possibly, an intron was lost in *ERK* as a result of reverse transcription of a partially processed pre-mRNA that was re-inserted downstream from a promoter sequence. A similar mechanism of intron loss has been implicated in the rat preproinsulin I gene (Soares *et al.*, 1985).

We have used genomic DNAs from the human *EEK* and *ERK* genes and from 14 human-mouse somatic cell hybrids to localize *EEK* and *ERK* within the human genome. A DNA probe which hybridized specifically with the *EEK* gene, h*EEK*.D2p, detected a single PstI fragment only in hybrids containing human chromosome 1 (1.0 kb, Figure 3). Similarly, the h*ERK*.D12e probe which hybridized specifically with the *ERK* gene, detected a single PstI human fragment in the same hybrids (4.3 kb, Figure 3). As expected, mouse-specific fragments which hybridized to h*EEK*.D2p and h*ERK*.D12e were present in all hybrids (3.3 kb and 5.8 kb, respectively, Figure 3). Among all 14 hybrids, chromosome 1 showed 100% concordance with *EEK*

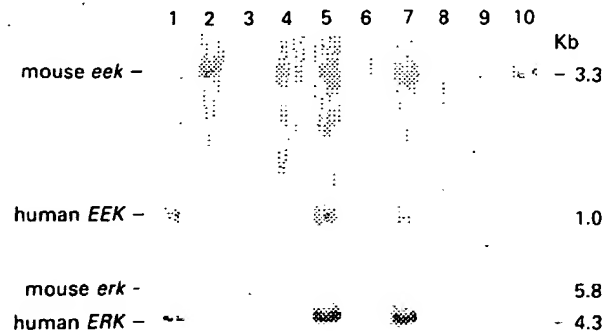


Figure 3 Southern blot analysis of the human *EEK* and *ERK* genes in somatic cell hybrids. Genomic DNA from human (lane 1), mouse (lane 2) and human-mouse hybrid (lanes 3-10) cell lines was digested with PstI and hybridized with human *EEK* DNA (h*EEK*.D2p, top) or with human *ERK* DNA (h*ERK*.D12e, bottom). Human chromosome 1 and the human DNA fragments hybridizing to *EEK* (1.0 kb) or to *ERK* (4.3 kb) are concordantly present (lanes 3, 5, 7) or absent (lanes 4, 6, 8-10).

method using the Klenow fragment of DNA polymerase (Sanger *et al.*, 1977), with ambiguities resolved using the modified T7 DNA polymerase and dITP (Tabor & Richardson, 1987; Sequenase, USB).

Southern and Northern blot analysis

Genomic DNAs from human leukocytes, cultured human fibroblasts, mouse fibroblasts or human-mouse somatic cell hybrids (Shier *et al.*, 1990; Watt & Willard, 1990) were digested with restriction endonucleases and size fractionated on 1% agarose gels before transfer to filters (Southern, 1975; Towbin *et al.*, 1979). Poly (A) RNA (2 µg), extracted using guanidine thiocyanate (Chirgwin *et al.*, 1979) and fractionated on an oligo(dT) column, was separated on a 1% formaldehyde-

agarose gel (Lehrach *et al.*, 1977) and transferred to nitrocellulose (Thomas, 1980). Rat kidney ribosomal RNA was used as size markers. Filters were hybridized and washed as described above.

Acknowledgements

We thank S.M. Blaine and S. Runciman for technical assistance; M. Shales for computer assistance; V. Auld and R. Dunn for the rat brain *lgt11* library; H.F. Willard for the generous gift of genomic DNAs from human-mouse somatic cell hybrids; K. Letwin and T. Pawson for the gift of the rat *erk* cDNA probe; and C.J. Ingles, T. Pawson, J. Segall, and H.F. Willard for helpful discussions and critical review of this manuscript. This work was supported by the Medical Research Council of Canada.

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Pasquale et al., Cell Regulation 2(7)523-34, July 1991

Chan et al., Oncogene 6(6)1057-61, 1991

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